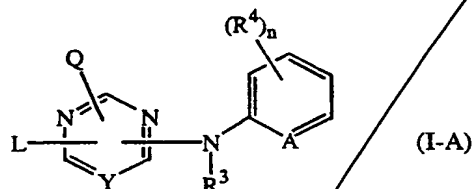


Claims

1. A particle consisting of a solid dispersion comprising
(a) a compound of formula



a N-oxide, a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof, wherein

Y is CR⁵ or N;

A is CH, CR⁴ or N;

n is 0, 1, 2, 3 or 4;

Q is -NR¹R² or when Y is CR⁵ then Q may also be hydrogen;

R¹ and R² are each independently selected from hydrogen, hydroxy, C₁₋₁₂alkyl,

C₁₋₁₂alkyloxy, C₁₋₁₂alkylcarbonyl, C₁₋₁₂alkyloxycarbonyl, aryl, amino, mono- or di(C₁₋₁₂alkyl)amino, mono- or di(C₁₋₁₂alkyl)aminocarbonyl wherein each of the

aforementioned C₁₋₁₂alkyl groups may optionally and each individually be substituted with one or two substituents each independently selected from hydroxy, C₁₋₆alkyloxy, hydroxy C₁₋₆alkyloxy, carboxyl, C₁₋₆alkyloxycarbonyl, cyano, amino, imino, aminocarbonyl, aminocarbonylamino, mono- or di(C₁₋₆alkyl)amino, aryl and Het; or

R¹ and R² taken together may form pyrrolidinyl, piperidinyl, morpholinyl, azido or mono- or di(C₁₋₁₂alkyl)aminoC₁₋₄alkylidene;

R³ is hydrogen, aryl, C₁₋₆alkylcarbonyl, C₁₋₆alkyl, C₁₋₆alkyloxycarbonyl, C₁₋₆alkyl substituted with C₁₋₆alkyloxycarbonyl; and

each R⁴ independently is hydroxy, halo, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, amino-

carbonyl, nitro, amino, trihalomethyl, trihalomethyloxy, or when Y is CR⁵ then R⁴ may also represent C₁₋₆alkyl substituted with cyano or aminocarbonyl;

R⁵ is hydrogen or C₁₋₄alkyl;

L is -X¹-R⁶ or -X²-Alk-R⁷ wherein

R⁶ and R⁷ each independently are phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy, C₁₋₆alkyl, C₁₋₆alkyloxy, C₁₋₆alkylcarbonyl, C₁₋₆alkyloxycarbonyl, formyl, cyano, nitro, amino, and trifluoromethyl; or when Y is CR⁵ then R⁶ and R⁷ may also be selected from phenyl substituted with one, two, three, four or five substituents each independently selected from aminocarbonyl, trihalomethyloxy

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and trihalomethyl; or when Y is N then R⁶ and R⁷ may also be selected from indanyl or indolyl, each of said indanyl or indolyl may be substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy, C₁₋₆alkyl, C₁₋₆alkyloxy, C₁₋₆alkylcarbonyl, C₁₋₆alkyloxycarbonyl, formyl, cyano, nitro, amino, and trifluoromethyl;

X¹ and X² are each independently -NR³-, -NH-NH-, -N=N-, -O-, -S-, -S(=O)- or -S(=O)₂-;

Alk is C₁₋₄alkanediyl; or

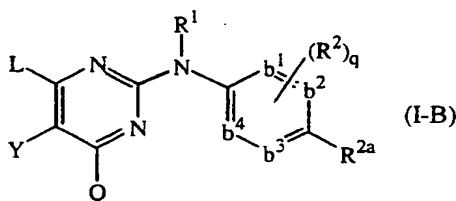
when Y is CR⁵ then L may also be selected from C₁₋₁₀alkyl, C₃₋₁₀alkenyl, C₃₋₁₀alkynyl, C₃₋₇cycloalkyl, or C₁₋₁₀alkyl substituted with one or two substituents independently selected from C₃₋₇cycloalkyl, indanyl, indolyl and phenyl, wherein said phenyl, indanyl and indolyl may be substituted with one, two, three, four or where possible five substituents each independently selected from halo, hydroxy, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, aminocarbonyl, C₁₋₆alkyloxycarbonyl, formyl, nitro, amino, trihalomethyl, trihalomethyloxy and C₁₋₆alkylcarbonyl;

aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, nitro and trifluoromethyl;

Het is an aliphatic or aromatic heterocyclic radical; said aliphatic heterocyclic radical is selected from pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl and tetrahydrothienyl wherein each of said aliphatic heterocyclic radical may optionally be substituted with an oxo group; and said aromatic heterocyclic radical is selected from pyrrolyl, furanyl, thienyl, pyridyl, pyrimidinyl, pyrazinyl and pyridazinyl wherein each of said aromatic heterocyclic radical may optionally be substituted with hydroxy;

or

a compound of formula



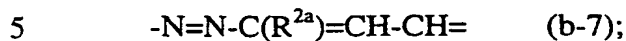
the N-oxides, the pharmaceutically acceptable addition salts, quaternary amines and the stereochemically isomeric forms thereof, wherein

-b¹=b²-C(R^{2a})=b³-b⁴= represents a bivalent radical of formula

-CH=CH-C(R^{2a})=CH-CH= (b-1);

-N=CH-C(R^{2a})=CH-CH= (b-2);

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q is 0, 1, 2; or where possible q is 3 or 4;

R^1 is hydrogen, aryl, formyl, C_{1-6} alkylcarbonyl, C_{1-6} alkyl, C_{1-6} alkyloxycarbonyl,

C_{1-6} alkyl substituted with formyl, C_{1-6} alkylcarbonyl, C_{1-6} alkyloxycarbonyl;

R^{2a} is cyano, aminocarbonyl, mono- or di(methyl)aminocarbonyl, C_{1-6} alkyl substituted

with cyano, aminocarbonyl or mono- or di(methyl)aminocarbonyl, C_{2-6} alkenyl

substituted with cyano, or C_{2-6} alkynyl substituted with cyano;

each R^2 independently is hydroxy, halo, C_{1-6} alkyl optionally substituted with cyano or

$-\text{C}(=\text{O})\text{R}^6$, C_{3-7} cycloalkyl, C_{2-6} alkenyl optionally substituted with one or more

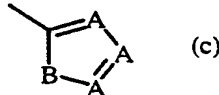
halogen atoms or cyano, C_{2-6} alkynyl optionally substituted with one or more

halogen atoms or cyano, C_{1-6} alkyloxy, C_{1-6} alkyloxycarbonyl, carboxyl, cyano,

nitro, amino, mono- or di(C_{1-6} alkyl)amino, polyhalomethyl, polyhalomethyloxy,

polyhalomethylthio, $-\text{S}(=\text{O})_p\text{R}^6$, $-\text{NH}-\text{S}(=\text{O})_p\text{R}^6$, $-\text{C}(=\text{O})\text{R}^6$, $-\text{NHC}(=\text{O})\text{H}$,

$-\text{C}(=\text{O})\text{NHNH}_2$, $-\text{NHC}(=\text{O})\text{R}^6$, $-\text{C}(=\text{NH})\text{R}^6$ or a radical of formula



wherein each A independently is N, CH or CR^6 ;

B is NH, O, S or NR^6 ;

p is 1 or 2; and

R^6 is methyl, amino, mono- or dimethylamino or polyhalomethyl;

L is C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, whereby each of said

aliphatic group may be substituted with one or two substituents independently selected from

* C_{3-7} cycloalkyl,

* indolyl or isoindolyl, each optionally substituted with one, two, three or four substituents each independently selected from halo, C_{1-6} alkyl, hydroxy,

C_{1-6} alkyloxy, cyano, aminocarbonyl, nitro, amino, polyhalomethyl,

polyhalomethyloxy and C_{1-6} alkylcarbonyl,

* phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R^2 ; or

L is $-\text{X}-\text{R}^3$ wherein

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~~R³ is phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R²; and X is -NR¹-, -NH-NH-, -N=N-, -O-, -C(=O)-, -CHOH-, -S-, -S(=O)- or -S(=O)₂-;~~

5 Q represents hydrogen, C₁₋₆alkyl, halo, polyhaloC₁₋₆alkyl or -NR⁴R⁵; and

R⁴ and R⁵ are each independently selected from hydrogen, hydroxy, C₁₋₁₂alkyl, C₁₋₁₂alkyloxy, C₁₋₁₂alkylcarbonyl, C₁₋₁₂alkyloxy carbonyl, aryl, amino, mono- or di(C₁₋₁₂alkyl)amino, mono- or di(C₁₋₁₂alkyl)aminocarbonyl wherein each of the aforementioned C₁₋₁₂alkyl groups may optionally and each individually be substituted with one or two substituents each independently selected from hydroxy, C₁₋₆alkyloxy, hydroxyC₁₋₆alkyloxy, carboxyl, C₁₋₆alkyloxy carbonyl, cyano, amino, imino, mono- or di(C₁₋₆alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, -S(=O)_pR⁶, -NH-S(=O)_pR⁶, -C(=O)R⁶, -NHC(=O)H, -C(=O)NHNH₂, -NHC(=O)R⁶, -C(=NH)R⁶, aryl and Het; or

15 R⁴ and R⁵ taken together may form pyrrolidinyl, piperidinyl, morpholinyl, azido or mono- or di(C₁₋₁₂alkyl)aminoC₁₋₄alkylidene;

Y represents hydroxy, halo, C₃₋₇cycloalkyl, C₂₋₆alkenyl optionally substituted with one or more halogen atoms, C₂₋₆alkynyl optionally substituted with one or more halogen atoms, C₁₋₆alkyl substituted with cyano or -C(=O)R⁶, C₁₋₆alkyloxy, C₁₋₆alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di(C₁₋₆alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, -S(=O)_pR⁶, -NH-S(=O)_pR⁶, -C(=O)R⁶, -NHC(=O)H, -C(=O)NHNH₂, -NHC(=O)R⁶, -C(=NH)R⁶ or aryl;

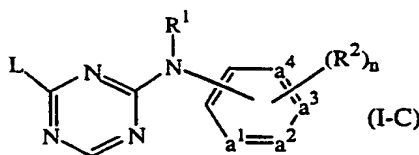
25 aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, C₁₋₆alkyl, C₃₋₇cycloalkyl, C₁₋₆alkyloxy, cyano, nitro, polyhaloC₁₋₆alkyl and polyhaloC₁₋₆alkyloxy;

Het is an aliphatic or aromatic heterocyclic radical; said aliphatic heterocyclic radical is selected from pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl and tetrahydrothienyl wherein each of said aliphatic heterocyclic radical may optionally be substituted with an oxo group; and said aromatic heterocyclic radical is selected from pyrrolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl wherein each of said aromatic heterocyclic radical may optionally be substituted with hydroxy;

or

35 a compound of formula

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the *N*-oxides, the pharmaceutically acceptable addition salts, quaternary amines and the stereochemically isomeric forms thereof, wherein

5 $-a^1=a^2-a^3=a^4-$ represents a bivalent radical of formula

$-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$ (a-1);

$-\text{N}=\text{CH}-\text{CH}=\text{CH}-$ (a-2);

$-\text{N}=\text{CH}-\text{N}=\text{CH}-$ (a-3);

$-\text{N}=\text{CH}-\text{CH}=\text{N}-$ (a-4);

10 $-\text{N}=\text{N}-\text{CH}=\text{CH}-$ (a-5);

n is 0, 1, 2, 3 or 4; and in case $-a^1=a^2-a^3=a^4-$ is (a-1), then *n* may also be 5;

*R*¹ is hydrogen, aryl, formyl, C₁₋₆alkylcarbonyl, C₁₋₆alkyl, C₁₋₆alkyloxycarbonyl,

C₁₋₆alkyl substituted with formyl, C₁₋₆alkylcarbonyl, C₁₋₆alkyloxycarbonyl; and

each *R*² independently is hydroxy, halo, C₁₋₆alkyl optionally substituted with cyano or

15 $-\text{C}(=\text{O})\text{R}^4$, C₃₋₇cycloalkyl, C₂₋₆alkenyl optionally substituted with one or more

halogen atoms or cyano, C₂₋₆alkynyl optionally substituted with one or more

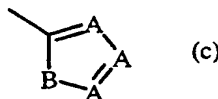
halogen atoms or cyano, C₁₋₆alkyloxy, C₁₋₆alkyloxycarbonyl, carboxyl, cyano, nitro,

amino, mono- or di(C₁₋₆alkyl)amino, polyhalomethyl, polyhalomethyloxy,

polyhalomethylthio,

20 $-\text{S}(=\text{O})_p\text{R}^4$, $-\text{NH}-\text{S}(=\text{O})_p\text{R}^4$, $-\text{C}(=\text{O})\text{R}^4$, $-\text{NHC}(=\text{O})\text{H}$, $-\text{C}(=\text{O})\text{NHNH}_2$,

$-\text{NHC}(=\text{O})\text{R}^4$, $-\text{C}(=\text{NH})\text{R}^4$ or a radical of formula



wherein each A independently is N, CH or CR⁴;

B is NH, O, S or NR⁴;

25 *p* is 1 or 2; and

*R*⁴ is methyl, amino, mono- or dimethylamino or polyhalomethyl;

L is C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₃₋₇cycloalkyl, whereby each of said aliphatic group may be substituted with one or two substituents independently selected from

30 * C₃₋₇cycloalkyl,

* indolyl or isoindolyl, each optionally substituted with one, two, three or four substituents each independently selected from halo, C₁₋₆alkyl, hydroxy,

C₁₋₆alkyloxy, cyano, aminocarbonyl, nitro, amino, polyhalomethyl, polyhalomethyloxy and C₁₋₆alkylcarbonyl,

- * phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R²; or

L is -X-R³ wherein

R³ is phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R²; and

X is -NR¹-, -NH-NH-, -N=N-, -O-, -C(=O)-, -CHOH-, -S-, -S(=O)- or -S(=O)₂-; aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, C₁₋₆alkyl, C₃₋₇cycloalkyl, C₁₋₆alkyloxy, cyano, nitro, polyhaloC₁₋₆alkyl and polyhaloC₁₋₆alkyloxy;

with the proviso that compounds wherein

- * L is C₁₋₃alkyl; R¹ is selected from hydrogen, ethyl and methyl; -a¹=a²-a³=a⁴- represents a bivalent radical of formula (a-1); n is 0 or 1 and R² is selected from fluoro, chloro, methyl, trifluoromethyl, ethyloxy and nitro; or
- * L is -X-R³, X is -NH-; R¹ is hydrogen; -a¹=a²-a³=a⁴- represents a bivalent radical of formula (a-1); n is 0 or 1 and R² is selected from chloro, methyl, methyloxy, cyano, amino and nitro and R³ is phenyl, optionally substituted with one substituent selected from chloro, methyl, methyloxy, cyano, amino and nitro;

and the compounds

- * N,N'-dipyridinyl-(1,3,5)-triazine-2,4-diamine;
- * (4-chloro-phenyl)-(4(1-(4-isobutyl-phenyl)-ethyl)-(1,3,5) triazin-2-yl)-amine

are not included;

and

(b) one or more pharmaceutically acceptable water-soluble polymers.

2. A particle according to claim 1 having a particle size of less than 1500 μm .
3. A particle according to claim 1 or 2 wherein the compound of formula (I-A), (I-B) or (I-C) is in a non-crystalline phase.
4. A particle according to claim 3 wherein the solid dispersion is in the form of a solid solution comprising (a) and (b), or in the form of a dispersion wherein amorphous or

microcrystalline (a) or amorphous or microcrystalline (b) is dispersed more or less evenly in a solid solution comprising (a) and (b).

5. A particle according to the preceding claims wherein the compound of formula (I-A), (I-B) or (I-C) is 4-[[4-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]amino]benzonitrile 4-[[4-amino-5-bromo-6-(4-cyano-2,6-dimethylphenoxy)-2-pyrimidinyl]amino]benzonitrile (R165335), 4-[[4-amino-5-chloro-6-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]amino]benzonitrile (, 4-[[5-chloro-4-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]amino]benzonitrile (4-[[5-bromo-4-(4-cyano-2,6-dimethylphenoxy)-2-pyrimidinyl]amino]benzonitrile (4-[[4-amino-5-chloro-6-[(4-cyano-2,6-dimethylphenyl)amino]-2-pyrimidinyl]amino]benzonitrile (4-[[5-bromo-6-[(4-cyano-2,6-dimethylphenyl)amino]-2-pyrimidinyl]amino]benzonitrile (4-[[4-amino-5-chloro-6-(4-cyano-2,6-dimethylphenoxy)-2-pyrimidinyl]amino]benzonitrile (4-[[2-[(cyanophenyl)amino]-4-pyrimidinyl]amino]-3,5-dimethylbenzonitrile (or 4-[[4-[(2,4,6-trimethylphenyl)amino]-1,3,5-triazin-2-yl]amino]benzonitrile .
6. A particle according to the preceding claims wherein the compound of formula (I-A) is 4-[[4-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]amino]benzonitrile .
7. A particle according to the preceding claims wherein the water-soluble polymer is a polymer that has an apparent viscosity of 1 to 5000 mPa.s when dissolved at 20°C in an aqueous solution at 2% (w/v).
8. A particle according to claim 7 wherein the water-soluble polymer is selected from the group comprising
- alkylcelluloses such as methylcellulose,
 - hydroxyalkylcelluloses such as hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose and hydroxybutylcellulose,
 - hydroxyalkyl alkylcelluloses such as hydroxyethyl methylcellulose and hydroxypropyl methylcellulose,
 - carboxyalkylcelluloses such as carboxymethylcellulose,
 - alkali metal salts of carboxyalkylcelluloses such as sodium carboxymethylcellulose,
 - carboxyalkylalkylcelluloses such as carboxymethylethylcellulose,
 - carboxyalkylcellulose esters,
 - starches,

- pectines such as sodium carboxymethylamyopectine,
- chitin derivates such as chitosan,
- di-, oligo- or polysaccharides such as trehalose, cyclodextrins or a derivative thereof, alginic acid, alkali metal and ammonium salts thereof, carrageenans, galactomannans, tragacanth, agar-agar, gummi arabicum, guar gummi and xanthan gummi,
- polyacrylic acids and the salts thereof,
- polymethacrylic acids, the salts and esters thereof, methacrylate copolymers,
- polyvinylalcohol,
- polyalkylene oxides such as polyethylene oxide and polypropylene oxide and copolymers of ethylene oxide and propylene oxide.

9. A particle according to claim 8 wherein the water-soluble polymer is hydroxypropyl methylcellulose HPMC 2910 5 mPa.s.

10. A particle according to claim 9 wherein the weight-by-weight ratio of (a) : (b) is in the range of 1 : 1 to 1 : 899.

11. A particle according to any one of the preceding claims obtainable by melt-extrusion of the components and grinding, and optionally sieving.

12. A particle according to any one of the previous claims consisting of a solid solution comprising two parts by weight of a compound of formula (I-A), (I-B) or (I-C) and three parts by weight of hydroxypropyl methylcellulose HPMC 2910 5 mPa.s, obtainable by blending said components, extruding the blend at a temperature in the range of 20°C - 300°C, grinding the extrudate, and optionally sieving the thus obtained particles.

13. A particle according to the preceding claims further comprising one or more pharmaceutically acceptable excipients.

14. A pharmaceutical dosage form comprising a therapeutically effective amount of particles as claimed in any one of the preceding claims.

15. A dosage form according to claim 14 adapted for oral administration shaped as a tablet.

16. A dosage form according to claim 15 for immediate release of a compound of formula (I-A), (I-B) or (I-C) upon oral ingestion wherein said particles are homogeneously distributed throughout a mixture of a diluent and a disintegrant.
17. A dosage form according to claim 15 or 16 surrounded by a film-coat comprising a film-forming polymer, a plasticizer and optionally a pigment.
18. A dosage form according to claim 16 wherein the diluent is a spray-dried mixture of lactose monohydrate and microcrystalline cellulose (75 : 25), and the disintegrant is croscopidone or croscarmellose.
19. A dosage form according to any one of claims 14 to 18 wherein the weight of said particles is at least 40 % of the total weight of the dosage form.
20. A process of preparing particles as claimed in any one of claims 1 to 13 characterized by blending the components, extruding said blend at a temperature in the range of 20 - 300 °C, grinding the extrudate, and optionally sieving the particles.
21. A process of preparing a pharmaceutical dosage form as claimed in any one of claims 14 to 18 characterized by blending a therapeutically effective amount of particles as claimed in any one of claims 1 to 13 with pharmaceutically acceptable excipients and compressing said blend into tablets or filling said blend in capsules.
22. Particles according to any one of claims 1 to 13 for use in preparing a pharmaceutical dosage form for oral administration to a mammal suffering from a viral infection, wherein a single such dosage form can be administered once daily to said mammal.
23. Use of particles according to any one of claims 1 to 13 for the preparation of a pharmaceutical dosage form for oral administration to a mammal suffering from a viral infection, wherein a single such dosage form can be administered once daily to said mammal.
24. A pharmaceutical package suitable for commercial sale comprising a container, an oral dosage form of a compound of formula (I-A), (I-B) or (I-C) as claimed in any one of claims 14 to 19, and associated with said package written matter.